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# Desymmetrization of a Centrosymmetric Diepoxide: Efficient Synthesis of a Key Intermediate in a Total Synthesis of Hemibrevetoxin B

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The preparation of an established intermediate in a total synthesis of hemibrevetoxin B is described. The acid-catalyzed cyclization of *trans*-4,5-epoxyoctane-2,7-dione exhibited a valuable mixture of kinetic and thermodynamic control: stereospecific epoxide opening was followed by equilibration of the products to provide the required *trans*-fused octahydropyrano[3,2-*b*]pyran ring system. Two-directional elaboration, by acetal substitution, ozonolysis, and sulfur ylide-mediated epoxidation, provided a centrosymmetric diepoxide. The key step of the synthesis was the first desymmetrization of a centrosymmetric molecule in natural product synthesis: Jacobsen asymmetric epoxide hydrolysis and acetonization provided the known synthetic intermediate in 97% yield and >95% ee over two steps. The exploitation of the center of symmetry of the AB ring system of the natural product contributed greatly to the efficiency (eight steps, 34% overall yield) of the synthesis.

## Introduction

Polycyclic ether marine natural products, such as the ciguatoxins (e.g. CTX1B, **1**), brevetoxins, and yessotoxin (**3**) (Chart 1), are potent neurotoxins that bind to a common site of, and activate, voltage-sensitive sodium channels.[1] These natural products originate from the "red tides" of marine unicellular algae that are responsible for the illness and death of human consumers of shellfish and the fatalities of marine mammals and other animals. The fascinating architecture of these marine natural products raises many challenges, such as the iterative synthesis of cyclic ethers and the control of the all *trans* stereochemistry of the ring junctions. Iterative methods, including two-directional approaches, have been developed for the synthesis of polycyclic ethers, involving, for example, ring-closing metathesis−hydroboration sequences[2] and the alkylation of α,β-epoxy sulfones.[3] Syntheses of hemibrevetoxin B[4−7] (**2**) and brevetoxin A[8] have been accomplished.

Many polycyclic ether natural products contain centrosymmetric fragments, such as the boxed fragments in the structures **1**−**3**, but this hidden symmetry has not been exploited in their synthesis. Nonetheless, the exploitation of hidden symmetry[9] can dramatically improve synthetic efficiency, especially when combined with a two-directional synthetic strategy.[10]

**Our approach to the epoxide 4**, a key intermediate in an established synthesis of hemibrevetoxin B, is summarized in Scheme 1.[11] The epoxide **4** has been synthesized in 22 steps and 14% overall yield from geranyl acetate and has been converted in 32 steps into hemibrevetoxin B by means of an elegant double tetrahydropyran (THP) → oxepane ring expansion.[5] We envisaged that **4** could be prepared by desymmetrization of the centrosymmetric diepoxide **5**. Of course, the use of

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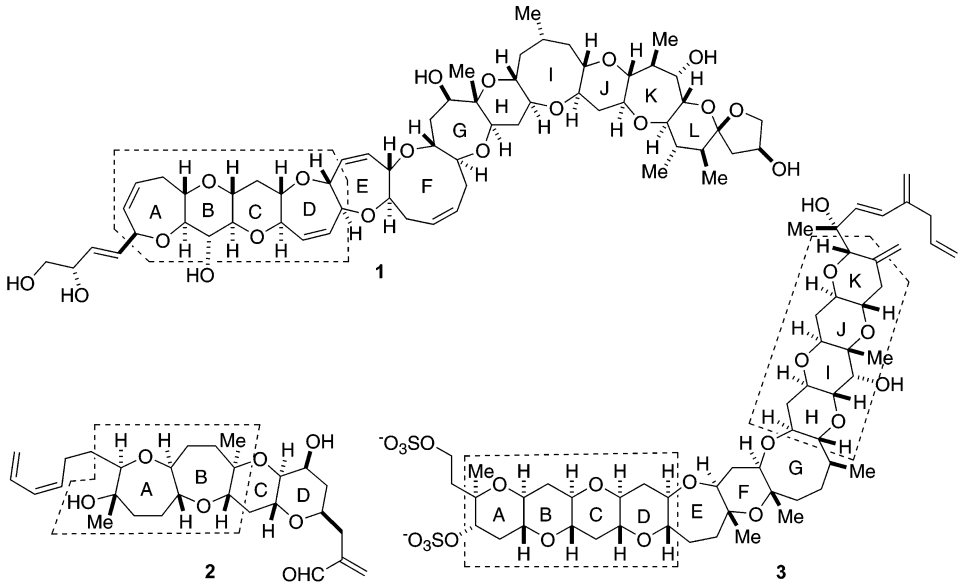
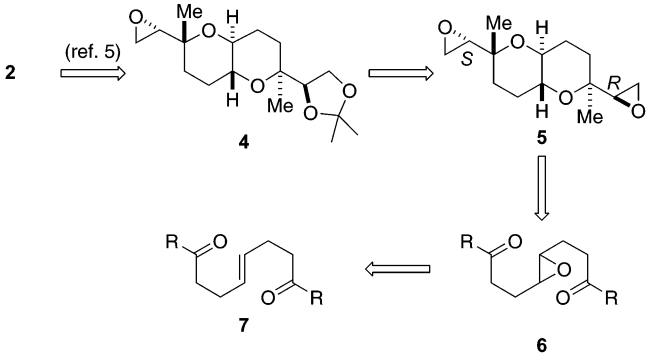
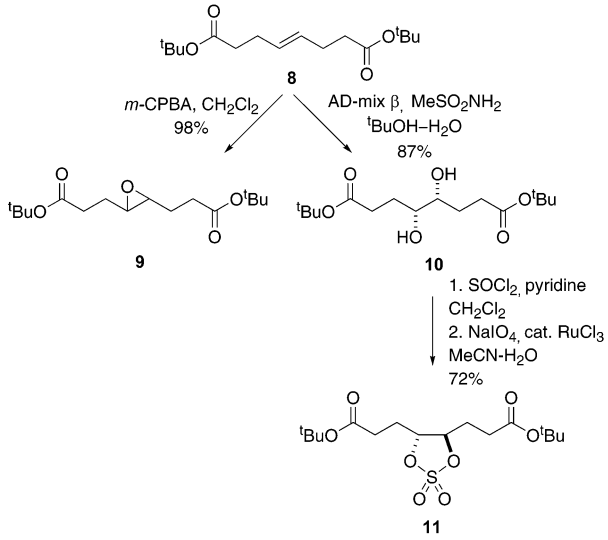
**CHART 1**



**SCHEME 1. Retrosynthetic Analysis**



**SCHEME 2. Synthesis of Cyclization Precursors**



an efficient desymmetrization,[12] rather than, for example, a kinetic resolution strategy, would enable the preparation of a high yield of either enantiomer of **4** in high enantiomeric excess. The desymmetrization of some centrosymmetric molecules has been reported previously: a [4 + 4]-photodimer[13] and a diketone[14] were desymmetrized by asymmetric reduction, and the enantioselective cleavage of a centrosymmetric lactide was exploited in the synthesis of syndiotactic polymers.[15]

The symmetry of the diepoxide **5** demanded that a two-directional synthetic approach was used. Furthermore, because **5** is not a chiral molecule, we felt obliged to control its relative stereochemistry using only achiral reagents. We planned to exploit the cyclization of an epoxy dicarbonyl compound **6**, synthesized from the corresponding alkene **7**, in the preparation of the di-THP ring system of **5**; the stereospecific opening of a *trans* epoxide **6** would install the required *trans* stereochemistry at the ring junction of **5**. It was planned that asymmetry would be introduced into the reaction sequence in the desymmetrization step using a single chiral catalytic reagent.

**Synthesis of the Cyclization Precursors.** The cyclization precursors were synthesized using the methods outlined in Schemes 2 and 3. Reaction of the lithium enolate of *tert*-butyl acetate with 0.5 equiv of *E*-1,4-dibromo-2-butene gave the unsaturated diester **8** in 51% yield. The diester **8** was converted into the corresponding epoxide **9** by epoxidation with *m*-CPBA (Scheme 2). Alternatively, asymmetric dihydroxylation[16] of the diester **8** (→**10**) with AD-mix $\beta$ and methanesulfonamide gave the optically active diol **10**; reaction of the diol **10** with thionyl chloride and oxidation under Sharpless' conditions[17] gave the optically active cyclic sulfate **11**. The enantiomeric excess of the diol **10** and the cyclic sulfate **11** were not determined.

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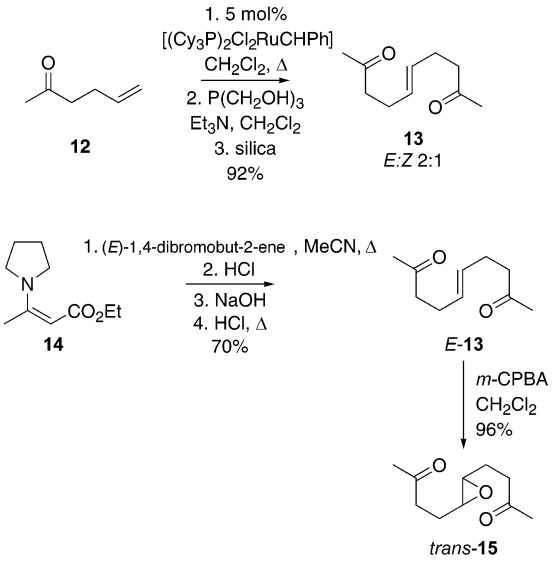
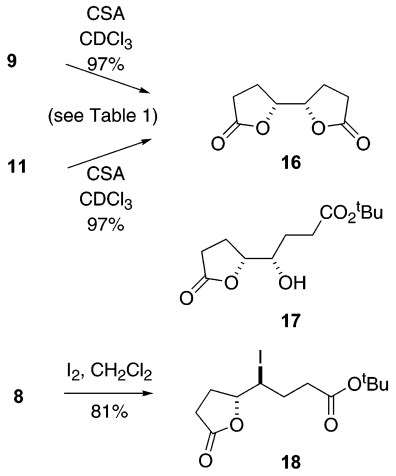
**SCHEME 3. Synthesis of Cyclization Precursors**




**SCHEME 4. Cyclization of the Diesters 8, 9, and 11**




Homo-metathesis of the γ,δ-unsaturated enone **12** and removal of the remaining ruthenium residues[18] gave the enedione **13** in 92% yield as a 2:1 mixture of *E* and *Z* geometric isomers (Scheme 3). Alternatively, the enedione **13** could be prepared as a single *E* isomer by allylation of the enamine **14**, hydrolysis of the enamine and the ester, and decarboxylation.[19] Epoxidation of the enedione *E*-**13** gave the *trans* epoxide **15** in high yield. A 2:1 mixture of the epoxides *trans*- and *cis*-**15** was also synthesized by epoxidation of a mixture of the enediones *E*- and *Z*-**13**.

**Cyclization Studies.** A study of the cyclization reactions of epoxides **6** and related compounds was initiated to identify conditions that led to the formation of the required *trans*-fused octahydropyrano[3,2-*b*]pyran (di-THP) ring system (Scheme 4 and Table 1). The cyclization of the epoxy diester **9** was catalyzed by camphorsulfonic acid and *p*-toluenesulfonic acid and gave only the known[20] di-γ-lactone **16** (entries 1 and 2a; Table 1); this result is unsurprising in view of the known preference[21] for 5-*exo* ring closure. A report suggested that the regiochemistry of the cyclizations of hydroxy cyclic sulfates might differ from those of the corresponding epoxides.[22] However, in the case of the cyclic sulfate **11**, the usual stereoelectronic preference for 5-*exo* ring closure was not overturned, and the same *meso*-dilactone **16** (which had $[\alpha]^{20}_D = 0$) was obtained (compare entry 2a with entries 2b and 2c, Table 1).

**TABLE 1. Cyclization Reactions of the Epoxide 10 and the Cyclic Sulfate 12**

| entry | starting material | reagent (equiv)[a] | temp (°C) | product(s)[b] |
|---|---|---|---|---|
| 1 | **9** | CSA (0.1) | 20 | **16**[c] |
| 2a | **9** | $TsOH·H_2O$ (1.5) | 20 | **16**[c] |
| 2b | **10** | $TsOH·H_2O$ (0.1) | 20 | **16**[c] |
| 2c | **10** | $TsOH·H_2O$ (0.1), MeCN | reflux | **16**[c] |
| 3a | **9** | $BF_3·OEt_2$ (1.1) | 20 | **16**[c] |
| 3b | **10** | $BF_3·OEt_2$ (0.1), MeCN | reflux | **16**[c] |
| 4a | **9** | $La(OTf)_3$ (1.1) | 20 | d |
| 4b | **9** | $La(OTf)_3$ (1.1) | 80 | **16**[c] |
| 4c | **10** | $La(OTf)_3$ (0.1), MeCN | reflux | **16**[c] |
| 5a | **9** | $MeAlCl_2$ (0.1) | 0 | **17**[c] |
| 5b | **9** | $MeAlCl_2$ (0.1) | 20 | **16**, **17**[e] |
| 6 | **9** | $SnCl_4$ (3.0) | 20 | **16**, **17**[f] |
| 7 | **9** | $ZnCl_2$ (0.1) | 20 | d |

[a] Reactions conducted in $CDCl_3$ unless otherwise stated. [b] The products were determined by analysis of the 300 MHz $^1H$ NMR spectra of the crude reaction mixtures. [c] Sole product by analysis of the 300 $^1H$ NMR spectrum of the crude reaction mixture. [d] No reaction. [e] 2:1 mixture of **16** and **17**. [f] 4:1 mixture of **16** and **17**.

A range of Lewis acids[23] were screened in an attempt to modify the natural regiochemistry of the cyclizations of **9** and **11** (entries 3−7, Table 1). In all cases where cyclization had occurred, the 5-*exo* mode of closure was observed. In some cases, the hydroxy ester **17** was observed as the kinetic product of the reaction (entries 5b and 6).

An alternative approach would involve the ring expansion of a γ-lactone to the corresponding δ-lactone. Accordingly, treatment of the unsaturated diester **8** with iodine in chloroform resulted in iodolactonization to give the γ-lactone **18** (Scheme 4). Unfortunately, attempted ring expansion[24] of the iodo lactone **18** using bis(tributyltin)oxide gave a complex mixture of products.

The cyclization of the epoxy diketones **15** was, however, much more promising (Scheme 5). Treatment of the epoxy diketone *trans*-**15** with pyridinium *p*-toluenesulfonate in methanol initially gave the acetals **21**, which equilibrated to give the thermodynamically more stable centrosymmetric diacetal **19**.[25] In a separate experiment, a 2:1 mixture of the epoxides *trans*- and *cis*-**15** was, under the same conditions, transformed into a 68:32 mixture of the acetals **19** and **22**, which were isolated in 57% and 28% yield respectively. Taken together, these results suggest that the initial epoxide opening is kinetically controlled

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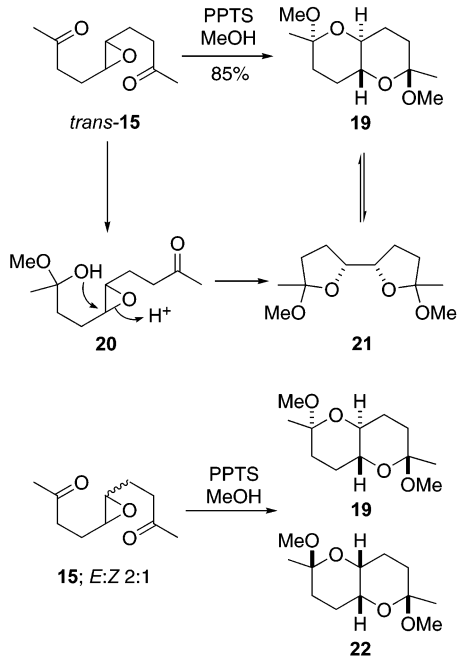
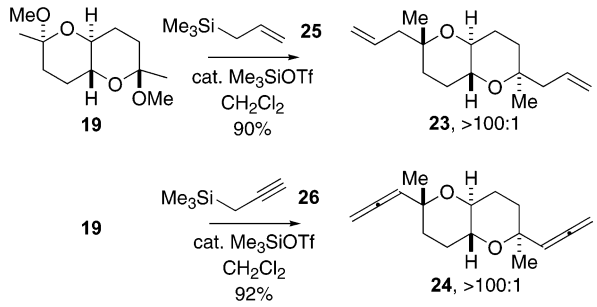
**SCHEME 5. Cyclization of the Epoxy Diketone 15**




**SCHEME 6. Two-Directional Acetal Substitution Reactions**




but that subsequent steps are thermodynamically controlled. Hence, general acid catalyzed 5-*exo* epoxide opening (**20** arrows) is, presumably, stereospecific and determines the relative stereochemistry of the ring junction. The diastereoisomeric acetals that were isolated (**19** and **22**) were those in which anomeric stabilization[26] is maximized and, in the case of the $C_2$-symmetric product **22**, unfavorable 1,3-diaxial interactions are minimized.

**Two-Directional Synthesis of the Centrosymmetric Diepoxide 5.** The two-directional nucleophilic substitution of the diacetal **19** was investigated using a range of nucleophiles (Scheme 6, Table 2). The reaction of **19** with the allylic silane[27] **25** (→**23**) was most effective when 10 mol % $Me_3SiOTf$ was used as the catalyst (compare entries 1a−c, Table 2). Similarly, an excellent yield of the di-THP **24** was obtained under these conditions when the progargyl silane[28] **26** (→**24**) was used as the nucleophile. Bis(trimethylsilyl)acetylene[29] and vinyltrimethylsilane[27] were unreactive under these reaction conditions.

**TABLE 2. Two-Directional Nucleophilic Substitution Reactions of the Diacetal 19**

| entry | nucleophile | Lewis acid (equiv)[a] | product | yield[b](%) |
|---|---|---|---|---|
| 1a | **25** | $SnCl_4$ (4.0) | c | |
| 1b | **25** | $TiCl_4$ (2.2) | **23** | 71 |
| 1c | **25** | $Me_3SiOTf$ (0.1) | **23** | 90 |
| 2 | **26** | $Me_3SiOTf$ (0.1) | **24** | 92 |

[a] Reactions were conducted with 7 equiv of nucleophile at −78 °C in dry dichloromethane. [b] Yield of purified product. [c] No reaction.

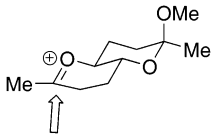


**FIGURE 1.** Stereoselective substitution of the diacetal **19**.

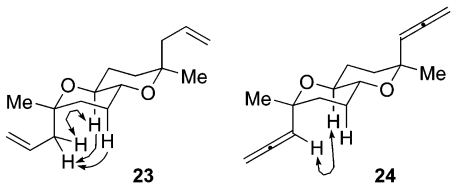
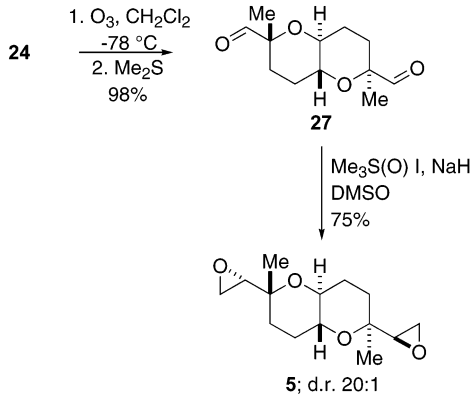



**FIGURE 2.** Diagnostic nuclear Overhauser enhancements for the centrosymmetric di-THPs **23** and **24**.

**SCHEME 7. Two-Directional Synthesis of the Centrosymmetric Diepoxide 5**




The nucleophilic substitutions of the diacetal **19** using the nucleophiles **25** and **26** gave the centrosymmetric di-THPs **23** and **24**, respectively, in which the nucleophile had attacked the intermediate oxonium ion from an axial direction (Figure 1).[30] The stereochemistry of the products **23** and **24** was determined using a series of NOE experiments (Figure 2). In the context of two-directional synthesis, the isolation of >100:1 mixtures of diastereoisomers must reflect >200:1 stereoselectivity in each acetal substitution reaction.

Ozonolysis of the diallene **24**, with reductive workup, gave the dialdehyde **27** (Scheme 7). The observation of a long-range coupling ($^4J$ = 1.6 Hz) between the aldehyde

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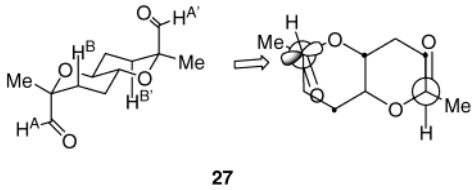


27

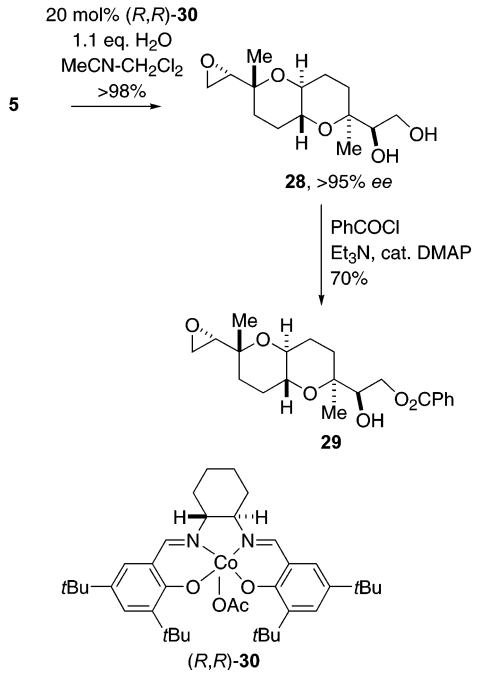
**FIGURE 3.** Ground-state and reactive conformations of the dialdehyde **27**.

proton ($H^A$) and the axial proton on C-3 ($H^B$) suggests that **27** largely populates the conformation with a W-arrangement between $H^A$ and $H^B$ (Figure 3). It has previously been shown that [1,4]dioxanes with an axial 2-aldehyde substituent have similar conformation preferences and undergo highly diastereoselective addition reactions.[31] Treatment of the dialdehyde **27** with dimethylsulfoxonium ylide gave the diepoxide **5** as a 20:1 mixture of centrosymmetric and unsymmetrical diastereoisomers. The reaction involving dimethylsulfonium ylide was significantly less diastereoselective and gave a 3:1 mixture of diastereoisomers. The stereoselectivity of these reactions may be rationalized in terms of attack of the ylides on the Felkin−Anh[32] conformation depicted in Figure 3. An alternative explanation may be that addition to the aldehydes is reversible and that the product-determining step may be a bond rotation to give the *transoid* betaine required for epoxide formation. It is possible that the rate-determining step, and hence the source of the diastereoselectivity, of the epoxidation reaction may depend on the reagent used.[33]

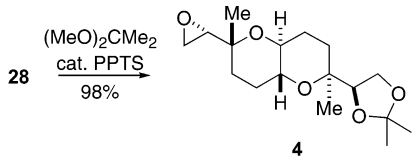
**Desymmetrization of the Centrosymmetric Bisepoxide 5.** A wide range of solvents (toluene, THF,[34a] 2-propanol, diethyl ether,[34b] dichloromethane, *tert*-butyl methyl ether,[34c,d] hexane-1,2-diol) were screened for the desymmetrization of the centrosymmetric bisepoxide **5** by Jacobsen enantioselective epoxide hydrolysis[35] (Scheme 8). In most of these cases, the reaction was extremely sluggish, presumably reflecting the insolubility of **5** above ca. 0.5 M in most organic solvents and the second-order dependence[36] of the rate of hydrolysis on the concentration of the catalyst. However, under optimized reaction conditions [20 mol % (*R*,*R*)-**30**, 1.0 M in 1:1 acetonitrile−dichloromethane[34e]], the desymmetrization was remarkably effective: the diol **28** was obtained in >98% yield after 4 days.

The diol **28** and its enantiomer *ent*-**28**, synthesized in >98% yield by desymmetrization of **5** using the enantiomeric catalyst (*S*,*S*)-**30**, were (separately) converted into the benzoate esters **29** and *ent*-**29** (Scheme 8). The enantiomeric excess of **29**, and hence **28**, was determined

**SCHEME 8. Desymmetrization of the Centrosymmetric Bisepoxide 5**




**SCHEME 9. Preparation of an Established Intermediate in the Synthesis of Hemibrevetoxin B**




by chiral analytical HPLC; the chromatogram was compared with that of a sample of low enantiomeric excess prepared by mixing the enantiomers of **29**. The benzoate ester **29** was found to have >95% ee, indicating that the desymmetrization reaction had been highly enantioselective. The diol **28** was converted into the known acetonide **4** (Scheme 9) [$[\alpha]^{20}_D = -21.7$ (*c*. = 0.67 in $CHCl_3$)], which was spectroscopically identical[5] to that prepared previously [lit.[5] $[\alpha]^{20}_D = -22.2$ (*c*. = 1.15 in $CHCl_3$)]. The sense of asymmetric induction was the same as those reported in the kinetic resolution of terminal epoxides.[35]

## Summary

A two-directional approach was exploited in the preparation of a known synthetic intermediate in a total synthesis of hemibrevetoxin B. The key step of our synthesis was the desymmetrization of a centrosymmetric molecule, a strategy that had not previously been exploited in natural product synthesis. Enantioselective hydrolysis of the bisepoxide **5**, synthesized using only achiral reagents to control its stereochemistry, was highly efficient: the diol **28** was obtained in >98% yield and with >95% ee. The exploitation of the symmetry of the centrosymmetric AB ring system contributed greatly to synthetic efficiency, enabling **4** to be prepared in eight

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steps and 34% overall yield from readily available starting materials.

## Experimental Section

General experimental methods have been previously described.[37]

**(*E*)-Dec-5-ene-2,9-dione (13).** A solution of 1,4-dibromobut-2-ene (1.0 g, 4.7 mmol) in acetonitrile (20 mL) was added dropwise to a solution of the enamine **14** (1.97 g, 10.8 mmol) in dry acetonitrile (20 mL). The reaction mixture was refluxed for 17 h, the solvent removed under reduced pressure, aqueous hydrochloric acid (25 mL, 1.0 M) added, and the reaction mixture heated at 100 °C for 2 h. The reaction mixture was extracted with diethyl ether (5 × 25 mL), and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Aqueous sodium hydroxide solution (20 mL, 2.5 M) was added, the reaction mixture was stirred for 20 h at room temperature, aqueous hydrochloric acid was added (20 mL, 2.5 M), and the solution was heated at 50 °C for 2 h. After cooling, the reaction mixture was extracted with dichloromethane (3 × 25 mL), washed with saturated sodium bicarbonate solution (2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a crude product that was purified by flash column chromatography, eluting with 1:1 EtOAc−petrol, to give *trans*-**13** (0.55 g, 70%): colorless needles; mp 36.8−37.6 °C (from EtOAc−petrol); $R_f$ 0.44 (EtOAc−petrol, 1:1); IR (Nujol mull) 2921, 1708, 1436, 1257, 1164, and 964 $cm^{-1}$; $^1H$ NMR (300 MHz; $CDCl_3$) $\delta$ 5.43 (m, 2H, 5-H and 6-H), 2.48 (t, *J* 7.3 Hz, 4H, 4-H and 7-H), 2.25 (m, 4H, 3-H and 8-H), and 2.14 (s, 6H, 1-H and 10-H); $^{13}C$ NMR (75 MHz; $CDCl_3$) $\delta$ 207.5, 129.8, 43.7, 31.4, and 27.0; *m*/*z* (EI) 168 (2%, $M^+$) and 110 (100). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6. Found: C, 71.2; H, 9.7.

**Dec-5-ene-2,9-dione (13).** Bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (105 mg, 0.13 mmol) was dissolved in dichloromethane (20 mL), 5-hexen-2-one (0.6 mL, 5.1 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. Dichloromethane (20 mL), triethylamine (1 mL), and tris(hydroxymethyl)phosphine (0.5 g, 4.0 mmol) were added, and the solution was stirred for 15 min. Silica (10 g) was added, the reaction mixture was stirred for 15 min, the silica was filtered and washed with ethyl acetate (20 mL), and the combined organic fractions were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product that was purified by flash column chromatography, eluting with 1:1 EtOAc−petrol, to give **13** (0.77 g, 92%; *E*:*Z* 2:1) as colorless needles. The major isomer was spectroscopically identical to that obtained previously.

**(5*R**,6*R**)-5,6-Epoxydecane-2,9-dione (15).** *m*-CPBA (0.12 g, 0.7 mmol) was added to a solution of *E*-**13** (0.1 g, 0.6 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h, washed with saturated aqueous sodium metabisulfite solution (2 × 20 mL) and saturated sodium bicarbonate solution (2 × 20 mL), and the combined organic fractions were dried ($MgSO_4$) and evaporated under reduced pressure to give *trans*-**15** (0.13 g, 96%) as colorless plates: mp 91.3−92.8 °C (from EtOAc−petrol); $R_f$ 0.57 (EtOAc−petrol, 1:9); IR (Nujol mull) 3399, 2984, 2949, 2849, 1760, 1703, 1488, 1430, 1353, 1244, 1169, 915, 862, and 818 $cm^{-1}$; $^1H$ NMR (300 MHz; $CDCl_3$) $\delta$ 2.75 (t, *J* 7.1 Hz, 2H, 5-H and 6-H), 2.57 (m, *J* 7.1 Hz, 4H, 3-H and 8-H), 2.17 (s, 6H, 1-H and 10-H), 1.94 (dq, *J* 13.1, 7.1 Hz, 2H, 4-$H_A$ and 7-$H_A$), and 1.66 (dq, *J* 13.1, 7.1 Hz, 2H, 4-$H_B$ and 7-$H_B$); $^{13}C$ NMR (75 MHz; $CDCl_3$) $\delta$ 208.0, 58.3, 39.8, 26.1, and 21.5; HRMS (ES) calcd for $C_{10}H_{17}O_3$ (M + H) 185.1178, found 185.1179.

**(2*R*,4a*S*,6*S*,8a*R*)-2,6-Dimethoxy-2,6-dimethyloctahydropyrano[3,2-*b*]pyran (19).** Pyridinium *p*-toluenesulfonate (20 mg, 0.01 mmol) was added to a stirred solution of **15** (200 mg, 1.09 mmol) in methanol (20 mL). The reaction mixture was stirred for 5 h and evaporated under reduced pressure to give a crude product that was purified by flash column chromatography, eluting with 1:9 EtOAc−petrol, to give **19** (212 mg, 85%) as colorless needles: mp 109.6−109.9 °C (from EtOAc−petrol); $R_f$ 0.37 (EtOAc−petrol, 1:9); IR (Nujol mull) 2982, 2924, 2358, 2341, 1461, 1379, 1111, 1061, 917, 876, 844, and 740 $cm^{-1}$; $^1H$ NMR (300 MHz; $CDCl_3$) $\delta$ 3.30 (m, 2H, 4a−H and 8a−H), 3.22(s, 6H, OMe), 1.90 (ddd, *J* 12.6, 3.2, 1.3 Hz, 2H, 3-$H_{eq}$ and 7-$H_{eq}$), 1.81 (m, 2H, 4-$H_{eq}$ and 8-$H_{eq}$), 1.66 (m, 4H, 3-$H_{ax}$, 4-$H_{ax}$, 7-$H_{ax}$ and 8-$H_{ax}$), and 1.30 (s, 6H, Me); $^{13}C$ NMR (75 MHz; $CDCl_3$) $\delta$ 98.3, 70.3, 48.1, 35.9, 25.5, and 23.6; *m*/*z* (EI) 230 (1.2%, $M^+$), 115 (100). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.6; H, 9.6. Found: C, 62.4; H, 9.8.

**(2*R*,4a*S*,6*S*,8a*R*)-2,6-Dimethyl-2,6-dipropa-1′,2′-dienyloctahydropyrano[3,2-*b*]pyran (24).** Propargyltrimethylsilane (0.23 mL, 1.52 mmol) was added to a stirred solution of **19** (50 mg, 0.2 mmol) in dry dichloromethane (10 mL) at −78 °C, trimethylsilyl triflate (4.1 $\mu$L, 0.02 mmol) was added, and the reaction mixture was stirred for 1 h, poured into saturated aqueous ammonium chloride solution (20 mL), extracted with diethyl ether (2 × 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give a crude product that was purified by flash column chromatography, eluting with 1:9 EtOAc−petrol, to give **24** (49.2 mg, 92%) as colorless needles: mp 34.7−34.8 °C (from EtOAc−petrol); $R_f$ 0.72 (EtOAc−petrol, 1:9); IR (Nujol mull) 2975, 2935, 2873, 1640, 1455, 1377, 1259, 1086, 994, 912, and 876 $cm^{-1}$; $^1H$ NMR (300 MHz; $CDCl_3$) $\delta$ 5.10 (td, *J* 6.7, 1.2 Hz, 2H, 1′-H), 4.84 (dd, *J* 10.6, 6.8 Hz, 2H, 3′$H_A$), 4.79 (dd, *J* 10.6, 6.7 Hz, 2H, 3′-$H_B$), 3.33 (m, 2H, 4a-H and 8a-H), 1.96 (m, 2H, 3-$H_{eq}$ and 7-$H_{eq}$), 1.70−1.56 (m, 6H, 3-$H_{ax}$, 4-H, 7-$H_{ax}$ and 8-H), and 1.31 (s, 6H, Me); $^{13}C$ NMR (75 MHz; $CDCl_3$) $\delta$ 207.4, 96.1, 77.5, 74.4, 73.3, 34.2, 30.9, and 27.0; *m*/*z* (ES) 269 ($MNa^+$). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.0; H, 9.0. Found: C, 77.8; H, 9.1. The relative stereochemistry was confirmed by the observation of mutual NOEs between 1′-H and 4a-H/8a-H.

**(2*R*,4a*S*,6*S*,8a*R*)-2,6-Dimethyloctahydropyrano[3,2-*b*]-pyran-2,6-dicarbaldehyde (27).** Ozone was bubbled through a solution of **24** (50 mg, 0.2 mmol) in dichloromethane (10 mL) until a blue color persisted. The reaction mixture was purged with $O_2$ until the blue color disappeared, dimethyl sulfide (0.2 mL, 3 mmol) added, the reaction mixture stirred overnight and evaporated under reduced pressure to give a crude product that was purified by flash column chromatography, eluting with 3:7 EtOAc−petrol, to give **27** (42.3 mg, 98%) as colorless needles: mp 72−74 °C (from EtOAc−petrol); $R_f$ 0.2 (EtOAc−petrol, 1:9); IR (Nujol mull) 3418, 2935, 2359, 1728, 1624, 1435, 1199, 1128, 1076, 1062, 1028, and 790 $cm^{-1}$; $^1H$ NMR (500 MHz; $CDCl_3$) $\delta$ 9.61 (d, *J* 1.7 Hz, 2H, CHO), 3.12 (m, 2H, 4a-H and 8a-H), 2.27 (ddd, *J* 13.5, 3.9, 2.8 Hz, 2H, 3-$H_{eq}$ and 7-$H_{eq}$), 1.94 (m, 2H, 4-$H_{eq}$ and 8-$H_{eq}$), 1.52 (ddt, *J* 13.5, 3.9, 1.7 Hz, 2H, 3-$H_{ax}$ and 7-$H_{ax}$), 1.40 (m, 2H, 4-$H_{ax}$ and 8-$H_{ax}$), and 1.16 (s, 6H); $^{13}C$ NMR (75 MHz; $CDCl_3$) $\delta$ 205.1, 80.9, 75.1, 30.1, 27.4, and 23.3; *m*/*z* (ES) 249 ($MNa^+$).

**(2*R*,4a*S*,6*S*,8a*R*)-2,6-Dimethyl-2-(1*S*)-oxiranyl-6-(1*R*)-oxiranyloctahydropyrano[3,2-*b*]pyran (5).** A solution of trimethylsulfoxonium iodide (97 mg, 0.4 mmol) in DMSO (1.0 mL) was added to a solution of NaH (60% dispersion in oil, 18 mg, 0.4 mmol) in DMSO (1 mL), and the mixture stirred at room temperature for 30 min. A solution of **27** (40 mg, 0.2 mmol) in DMSO (1 mL) was added, and the reaction mixture was stirred for 60 min, poured into ice−water, extracted with EtOAc (3 × 10 mL), washed with saturated brine (2 × 10 mL), dried ($MgSO_4$), and evaporated to give a crude product that was purified by flash column chromatography, eluting with EtOAc, to give **5** (42 mg, 75%) as colorless needles: mp 78−80 °C (from EtOAc−petrol); $R_f$ 0.8 (EtOAc); IR (liquid film) 2936, 2360, 1631, 1258, 1079 and 914 $cm^{-1}$; $^1H$ NMR (300 MHz; $CDCl_3$) $\delta$ 3.49 (m, 2H, 4a-H and 8a-H), 3.10 (ddd, *J* 4.3, 2.8, 0.8 Hz, 2H, oxirane 1-H), 2.73 (t, *J* 4.5 Hz, 2H, oxirane 2-$H_A$), 2.49 (dd, *J* 4.7, 2.8, 2H, oxirane 2-$H_B$), 1.86 (m, 2H, 3-$H_{eq}$

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and 7-$H_{eq}$), 1.73 (m, 2H, 4-$H_{eq}$ and 8-$H_{eq}$), 1.63−1.52 (m, 4H, 3-$H_{ax}$, 4-$H_{ax}$, 7-$H_{ax}$ and 8-$H_{ax}$), 1.14 (s, 6H, Me); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 73.7, 72.9, 57.6, 43.6, 31.3, 27.5, and 26.4; HRMS (ES) calcd for $C_{14}H_{22}O_4Na$ (M + Na) 277.1416, found 277.1414.

**(2*S*,4a*R*,6*R*,8a*S*)-2,6-Dimethyl-6-(1*S*)-oxiranyloctahydropyrano[3,2-*b*]pyran-2-yl-(*R*)-ethane-1,2-diol (28).** (*R*,*R*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (7 mg, 0.01 mmol) was dissolved in toluene (1 mL), acetic acid (2 $\mu$L) was added, and the reaction mixture was stirred while open to air for 15 min and evaporated under reduced pressure. Dichloromethane (0.12 mL), acetonitrile (0.12 mL), **5** (30 mg, 0.1 mmol), and water (3.5 $\mu$L, 0.2 mmol) were added, the reaction mixture was stirred for 4 days, evaporated under reduced pressure, and purified by flash column chromatography, eluting with 1:20 methanol:dichloromethane, to give **28** (31 mg, >98%) as colorless needles: mp 101−103 °C (from EtOAc−petrol); $R_f$ 0.26 (MeOH:$CH_2Cl_2$, 1:20); $[\alpha]^{20}_D$ −17.6 (*c* 1.5, $CHCl_3$); IR (neat) 3398, 3940, 2360, 2342, 1456, 1258, 1076, 1022, and 912 cm$^{-1}$; $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 4.24 (dd, *J* 8.6, 3.7 Hz, 1H, C*H*OH), 3.79 (dd, *J* 11.2, 3.7 Hz, 1H, C$H_A$H$_B$OH), 3.58 (dd, *J* 11.2, 8.7 Hz, 1H, CH$_A$$H_B$OH), 3.51 (ddd, *J* 11.1, 9.4 4.6 Hz, 1H, 4a-H), 3.28 (ddd, *J* 11.1, 9.4, 4.6 Hz, 1H, 8a-H), 3.13 (ddd, *J* 4.3, 2.8, 0.9 Hz, 1H, oxirane 1-H), 2.74 (app t, *J* 4.6, 1H, oxirane 2-$H_A$), 2.48 (dd, *J* 4.7, 2.8, 1H, oxirane 2-$H_B$), 2.15 (m, 1H, 3-$H_{ax}$), 2.04 (m, 1H), 1.14 (s, 3H, Me), and 1.13 (s, 3H, Me); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 75.9, 74.1, 73.4, 72.0, 69.7, 63.4, 57.9, 43.7, 32.9, 31.3, 27.9, 26.7, 26.4, and 23.3; HRMS (ES) calcd for $C_{14}H_{24}O_5Na$ (M + Na) 295.1521, found 295.1533.

**Diol *ent*-(28).** By the same general methods, (*S*,*S*)-**30** and the epoxide **5** gave *ent*-**28** as colorless needles: $[\alpha]_D^{20}$ +17.4 (*c* 1.5, $CHCl_3$).

**5-[(2*S*,4a*R*,6*R*,8a*S*)-2,6-Dimethyl-6-(1*S*)-oxiranyloctahydropyrano[3,2-*b*]pyran-2-yl]-(*R*)-2,2-dimethyl[1,3]-dioxolane (4).** 2,2-Dimethoxypropane (39 $\mu$L, 0.3 mmol) and pyridinium *p*-toluenesulfonate (0.2 mg, 0.01 mmol) were added to a stirred solution of **28** (5.8 mg, 0.02 mmol) in $CDCl_3$ (1 mL), and the solution was stirred at room temperature for 30 min. Triethylamine (3 drops) was added, the reaction mixture was preabsorbed onto silica gel and purified by flash column chromatography, eluting with 30:70 EtOAc−petrol, to give **4** as colorless needles (6.5 mg, 98%); mp 86−88 °C (from EtOAc−petrol) (lit.[5] mp 83−84 °C); $R_f$ 0.31 (EtOAc−petrol, 30:70); $[\alpha]^{20}_D$ −21.7 (*c* 0.67, $CHCl_3$) [lit.[5] $[\alpha]^{20}_D$ = −22.2 (*c*. = 1.15 in $CHCl_3$)]; IR (neat) 2938, 1632, 1455, 1374, 1262, 1213, 1157, and 1078 cm$^{-1}$; $^1$H NMR (300 MHz; $CDCl_3$) $\delta$ 4.69 (t, *J* 6.7 Hz, 1H), 3.99 (dd, *J* 8.6, 7.0 Hz, 1H, C$H_A$H$_B$O), 3.94 (dd, *J* 8.6, 6.4 Hz, 1H, CH$_A$$H_B$O), 3.48 (ddd, *J* 10.8, 9.4 4.9 Hz, 1H, 4a-H), 3.26 (ddd, *J* 11.1, 9.4, 4.6 Hz, 1H, 8a-H), 3.10 (m, 1H, oxirane 1-H), 2.73 (app t, *J* 4.5 Hz, 1H, oxirane 2-$H_A$), 2.48 (dd, *J* 4.7, 2.8 Hz, 1H, oxirane 2-$H_B$), 2.05 (m, 1H, 3-$H_{ax}$), 1.73−1.84 (m, 3H), 1.56−1.68 (m, 3H), 1.45−1.52 (m, 1H), 1.42 (s, 3H, Me), 1.35 (s, 3H, Me), 1.14 (s, 3H, Me) and 1.10 (s, 3H, Me); $^{13}$C NMR (75 MHz; $CDCl_3$) $\delta$ 109.7, 74.4, 74.2, 73.7, 73.1, 72.0, 65.1, 57.4, 43.3, 32.8, 31.1, 27.7, 26.4, 26.3, 26.1, 24.9, and 23.1; HRMS (ES) calcd for $C_{17}H_{28}O_5Na$ (M + Na) 335.1834, found 335.1837.

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**Supporting Information Available:** Experimental details and characterization data are provided for compounds **8**−**11**, **14**, **16**−**18**, **22**, **23**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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